**Survivors at risk: Hodgkin lymphoma survivors at high risk of second cancers**

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Amit Sud speaks to Sebastian Dennis-Beron, Commissioning Editor.

Amit Sud is a clinical research fellow in Hematology at the Institute of Cancer Research, UK. He undertook his undergraduate medical training at the University of Manchester, gaining an honors degree. He completed his Masters in Medical Research at Manchester University, gaining a distinction. He continued his medical training in Manchester and London and started his specialization in Hematology in South West London. He was successful in obtaining a Cancer Research UK funded clinical research fellowship in Hematology under the supervision of Professor Richard Houlston at the Institute of Cancer Research. His current research focus is that of genetic susceptibility to Hodgkin lymphoma. He is a trainee member of the NCRI Lymphoma clinical studies group.

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1. Could you please provide a brief summary of your career to date?

I completed my undergraduate medical training at Manchester University (Manchester, UK) and also and also spent an extra year undertaking a masters in medical research. After this, I continued my medical training in Manchester. I moved to London to continue my general medical training and, then commenced my hematology specialist training here at the Royal Marsden and the Institute of Cancer Research, London, (UK). Two years ago, I began a PhD funded by Cancer Research UK at the Institute of Cancer Research (London, UK), supervised by Professor Richard Houlston.

1. What is your research focusing on at present?

My research looks specifically at genetic susceptibility to Hodgkin lymphoma, which is a particular cancer I am interested in, but also to other B cell tumors and B cell cancers. I utilize genetic, epidemiological and biological data with my overarching aim to try and understand Hodgkin lymphoma in further detail.

1. You were an author on a recent study demonstrating that Hodgkin lymphoma survivors are at high risk of secondary cancers – could you give our readers an outline of the study and its methodology?

Hodgkin lymphoma was one of the first cancers that the medical profession managed to obtain relatively high cure rates through treatment involving chemotherapy and radiotherapy[1]. What became apparent is that many patients who survived the Hodgkin lymphoma had a lot of long term significant complications such as second cancers and cardiovascular disease[2]. So over the past few decades, there have been a lot of studies trying to investigate the risk factors of developing these complications. In terms of second cancers, the excess risk observed in Hodgkin lymphoma survivors has been reported to be influenced by various factors including age of treatment, site and dose of radiotherapy, chemotherapy and smoking[3-10]. So what has been postulated, although not demonstrated through epidemiological studies, is the detailed impact of family history on the second cancer risk. So in collaboration with Lund University (Lund, Sweden) and the Deutsches Krebsforschungzentrum (Heidelberg, Germany), we were able to use the Swedish cancer family project database[11], to identify all Hodgkin lymphoma cases diagnosed between 1965 and 2012 and their relatives. This allows one to, first, know which of these patients developed a second cancer and also to determine family relationships between the individuals. This allows for calculation, in an unbiased manner, of the risk of second cancer in individuals with Hodgkin Lymphoma. That is calculated using the ‘standardized incidence ratio’ that takes into account population rates of cancer, age and sex match. We were then able to investigate the influence of a family history of cancer and concordant cancers. Therefore, if an individual has a relative with say lung cancer, what is the individual’s risk of developing lung cancer after getting Hodgkin Lymphoma? We also used epidemiological tools such as estimating cumulative incidence with competing risk and relative survival to understand the second cancer risk in individuals with Hodgkin Lymphoma[12].

1. What roles did familial history of cancer and radiotherapy during treatment of cancer have on the risk of developing secondary cancers, respectively?

Unfortunately we didn’t have data on treatment, so the study couldn’t address an interaction between say the specific type of treatment and the family history. However, our study examines the broad picture of second cancer risks in Hodgkin lymphoma patients. With regard to the influence of family history, our study shows that there is a 1.3 fold higher risk of a second cancer in Hodgkin Lymphoma patients who have a family history of cancer compared to those without a family history. That relationship is correlated with the number of first degree relatives affected. What I mean by that is, the great the number of first-degree relatives with cancer, the greater the risk of second cancer after Hodgkin lymphoma. With respect to the concordant cancer risk; there is a 3.3 fold, 2.1 fold and 1.8 fold increased risk of developing lung, colorectal and breast cancer, respectively, in Hodgkin lymphoma patients who have a family history compared to those who don’t have a family history of this specific cancer. The other interesting point is trying to understand the relative contribution of different risk factors. Firstly, the familial risk of developing lung cancer in the general population, secondly the risk of Hodgkin lymphoma patients developing lung cancer, and thirdly, the risk of Hodgkin Lymphoma patients who have got a family history of lung cancer, developing lung cancer. That allows one to investigate the contributions of these different components to the overall risk, and the paper demonstrates a greater than additive interaction between family history of lung cancer and Hodgkin lymphoma treatment. The greater than additive risk could be related to other risk factors, such as for example smoking.

1. Were there discrepancies in the risk of secondary cancer due to age or gender?

This is not a new finding; there have been quite a few publications previously looking at this, but age and sex do influence second cancer risk. Quite a striking example is the risk of breast cancer. In women diagnosed with Hodgkin lymphoma under the age of 35 years, the risk of developing breast cancer is six times greater than that of the general population. This contrasts with women diagnosed with Hodgkin lymphoma greater than 35 years where the risk of breast cancer does not appear to elevated when compared to the general population.

1. How could the results of the study lead to developments in preventative treatments for Hodgkin lymphoma survivors?

Currently, there are some screening initiatives. For example in the UK, young women diagnosed with Hodgkin Lymphoma undergoing mantle field radiotherapy do get screening for secondary breast cancer[13]. The article doesn’t specifically address that point but it may be the first bit of evidence to suggest that there are potentially individuals who, we can identify at high risk of developing a second cancer, who may benefit from screening. Over the decades there has been a move to use less radiotherapy and less chemotherapy when treating Hodgkin Lymphoma patients, and now the approach used is a risk adapted approach[14]. This means that when someone is diagnosed with Hodgkin lymphoma, one looks at the risk of the disease not being cured with treatment and the treatment is tailored based on that risk. So this information could possibly be used to help inform the risk adapted approach being used currently.

1. Moreover, what clinical impact do you think this research may have in terms of follow up for patients once in remission?

Hodgkin lymphoma patients are treated by an oncologist or haematologist and are discharged from clinic less than five years following treatment. What we know is that a lot of the complications of treatment occur after this five year period. I think it’s known but it’s important to emphasize that these individuals do have long term complications that other health professionals need to be aware of. Because they might not necessarily go back to their oncologist 10, 20 years down the line with a problem, other practitioners such as general practitioners should be aware of this second cancer risk, and when they see these patients. I think there are moves to increase communication between the various levels of care, certainly in clinics that I work in. When patients are discharged from clinics, a summary of care and some information is sent back to the general practitioner.

1. What are the next steps for the field of hematological oncology, given this new development?

As I mentioned before, I think it’s important to investigate what impact treatment has on this family history influence on second cancer risk. as well as the other risk factors such as smoking. That requires long term follow up data, good phenotype data and robust collection of data. What one needs to do, and there are a few papers in the UK investigating this, is to look at the efficacy of screening in these individuals to find out whether screening is beneficial. The final point is, it would be interesting to try and understand the biological basis behind the increased risk in individuals with a family history. It could be environmental, for example smoking or it could be genetic. It is possible there is variation within people’s genetic code that increase people’s risk of developing second cancer after having chemotherapy and radiotherapy, which I think would be an interesting area to explore[15].

1. Do you think more needs to be done to make patients more aware of that secondary risk or is this being done already?

I think it is being done, certainly from my practice and practices that I have seen that is something we discuss with our patients. I think it’s very difficult for individuals because obviously when they are diagnosed with Hodgkin lymphoma or any cancer for example, the priority for patients is to cure the cancer. It is difficult to think 20, 30 years later and I guess that’s one of the important roles of the oncologist; as a guardian for the patient. Hence, I think it is important to try and communicate this with the patients although I think it is a very difficult thing to discuss. Generally speaking, the research community is studying this realizing that this is an important topic that warrants further research and further intervention to try and reduce the second cancer incidence and improve outcomes for our patients. Certainly, for a lot of the cancers, lung, colorectal and breast cancer, survival is stage dependent, so trying to pick these up earlier, will hopefully improve survival of our patients with Hodgkin lymphoma. 10. As cure rates for cancers improve, will there be more of a focus on long-term survivor health for the oncology field as a whole? I think that is the case with many clinics now devoted to caring for long-term complications of cancer treatments. Furthermore, there are now established research programs that are examining long term second cancer risk and other risks such as cardiovascular risk complications, physiological complications that patients experience long after their treatment. I think it’s an important topic that we should all be aware of.

1. What do you hope to achieve in the next few years?

My interest is in genetic susceptibility and I hope to identify some new genetic factors that influence people’s risk of developing Hodgkin lymphoma. I hope to try and provide some biological insight into how genetic risk factors mediate their effects.

Closing statement: I would like to say that I’m very grateful to the collaboration we’ve established among the three institutes, which has allowed me as a scientist to try and answer an important question. I think it’s a good example of a collaboration that has resulted in something that will hopefully benefit people - although it certainly needs further research.

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